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DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

NEW OPPORTUNITIES FOR THE SYNTHESIS OF QUINOXALINE-SUBSTITUTED HETEROCYCLIC AND ARYL MOIETIES

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6.7-Difluoroquinoxaline (**I**) reacted with dimedone, indandione, and 3-methyl-1-phenylpyrazol-5-one in DMSO solution in the presence of acid to form mono-substituted products **IIa – c**. Heating **I** with resorcinol in EtOH in the presence of acid gave resorcinol derivative **IId**. 6.7-Difluoroquinoxaline in the presence of base reacted with 3-methyl-1-phenylmethylpyrazol-5-one to form dipyrazolylmethane **III** and tetrapyrazolylethane derivative **IV**. Heating products **IIa – c** with *N*-methylpiperazine produced 7-methylpiperazine derivatives **Va – c** of 2-substituted quinoxalines.

Keywords: 6.7-difluoroquinoxaline, reactions with nucleophiles.

Compounds with various types of biological activity have been found among quinoxaline derivatives [1, 2]. The quinoxaline derivatives quinoxidine and dioxidine have been used as antimicrobial agents [3]. A series of condensed quinoxalines were patented as anticancer drugs [4].

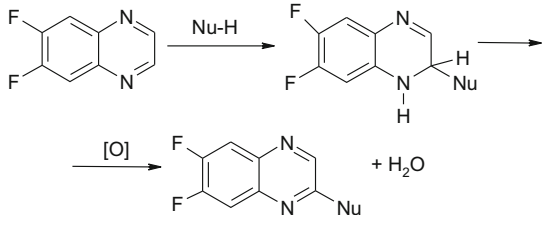
Substituted quinoxalines are synthesized either by condensation of the corresponding substituted *o*-phenylenediamines with 1.2-dioxo-derivatives or via substitution reactions of easily displaced functional groups in the quinoxaline core. Substitution reactions of F atoms in 6.7-difluoroquinoxalines with various nucleophiles were reported [5]. We recently described substitution reactions of hydrogen in the heterocyclic core of unsubstituted quinoxaline by several C-nucleophiles [6].

Herein we found that 6.7-difluoroquinoxaline (**I**) reacted with CH-acids such as dimedone, indandione, and 3-methyl-1-phenylmethylpyrazol-5-one in DMSO solution at room temperature in the presence of acid to form mono-substituted products **IIa – c** (Scheme 1).

Heating **I** with resorcinol in refluxing EtOH in the presence of HCl produced 4-(6.7-difluoroquinoxalin-2-yl)benzene-1.3-diol (**IId**).

The molecular weights of compounds **II** as determined by mass spectrometry agreed with the calculated values. A characteristic diagnostic signature in the PMR spectrum of mono-substituted products **II** was the presence of a separate resonance for the proton of the pyrazine ring at 9.0 – 10.5 ppm.

It was interesting that the described reactions of **I** with the C-nucleophiles did not stop at the formation of the σ-adducts but involved oxidation to the aromatic substitution products during the course of the reaction:



It is noteworthy that the described transformations of unsubstituted quinoxaline with the C-nucleophiles were simple and practically waste-free methods for producing

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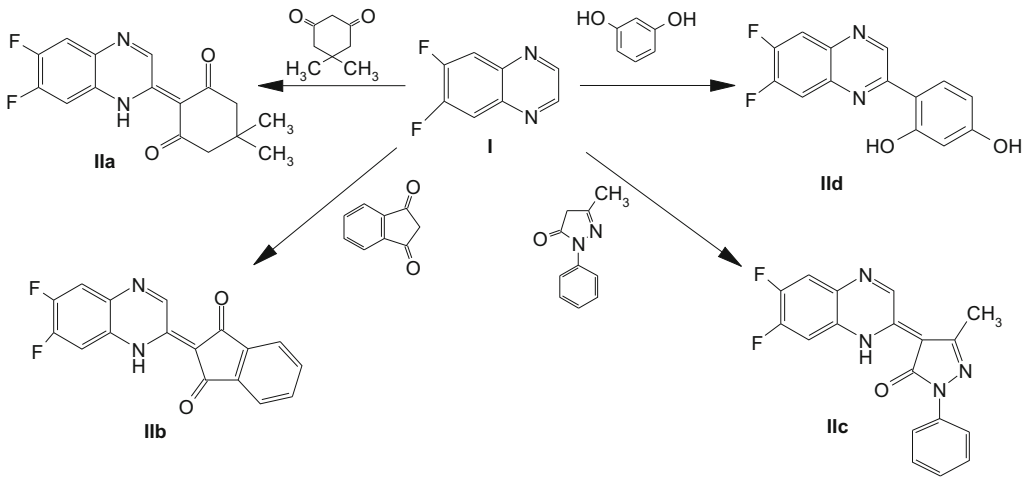
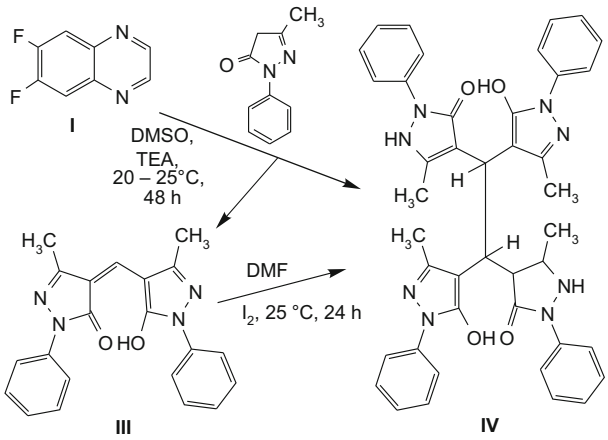
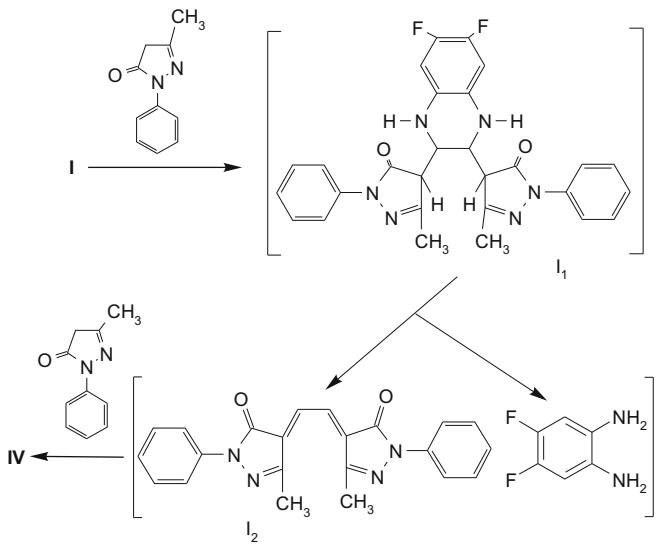
Scheme 1



Scheme 2



Scheme 3



mono-substituted quinoxaline derivatives with formation of H_2O as a result of the hydrogen substitution. The F atom in the aromatic quinoxaline ring did not undergo substitution.

Compound **I** reacted differently with 3-methyl-1-phenylmethylpyrazol-5-one in DMSO in the presence of base. Thus, the reaction of **I** with 3-methyl-1-phenylmethylpyrazol-5-one in DMSO in the presence of NEt_3 (TEA) produced the known dipyrazolylmethane (**III**) (Scheme 2) [7] and 4-[1,2-*bis*(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-(3-methyl-5-oxo-1-phenylpyrazolidin-4-yl)ethyl]-3-methyl-1-phenyl-1.2-dihydropyrazol-5-one (**IV**) [8].

It is noteworthy that brief heating of **IV** in refluxing DMF gave **III**. Product **IV** was transformed into **III** also in DMF solution in the presence of I_2 at room temperature. The transformation **IV** > **III** occurred also with brief heating of the crystals at 255 – 260°C.

The formation mechanism of **IV** from **I** apparently included the steps of nucleophilic addition of two molecules of 1-phenyl-3-methylpyrazol-5-one to the C=N bonds of quinoxaline to form *bis*-adduct $\mathbf{I_1}$ (Scheme 3) and cleavage of *bis*-adduct $\mathbf{I_1}$ to form intermediate $\mathbf{I_2}$ and subsequent transformation of the latter into **IV**.

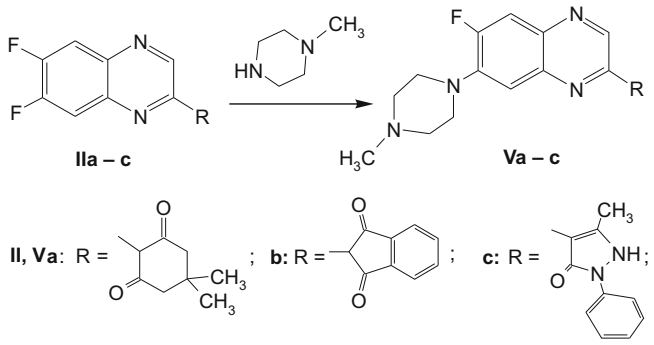
It is noteworthy that the synthesis of **III** and **IV** that was reported earlier [8] was carried out via the reaction of unsubstituted quinoxaline with 3-methyl-1-phenylpyrazol-5-one under conditions analogous to those described in the present work. This indicated that the F atoms located in the 6- and 7-positions of **I** had practically no effect on this transformation.

However, the presence in the aromatic core of such labile leaving groups as F atoms opened additional opportunities for synthesizing quinoxaline derivatives.

It was found during the course of the present work that products **IIa** – **c** reacted smoothly with *N*-methylpiperazine at 115 – 120°C in DMF solution to form the corresponding 7-methylpiperazino-derivatives of quinoxalines **Va** – **c** in 50 – 60% yields (Scheme 4).

The molecular weights of compounds **V** as determined by mass spectrometry corresponded with those calculated.

Scheme 4



Proof of localized F-7 substitution was obtained from studies of ^{1}H, ^{19}F, and ^{13}C NMR spectra of **IIa** and **Va**. The ^{13}C NMR spectrum of **IIa** contained resonances for nodal C-4a and C-8a as doublets of doublets as a result of coupling with two F atoms through three and four bonds with δ_C 136.32 ppm (J_{CF} 10.3 and 1.9 Hz) and δ_C 129.31 ppm (J_{CF} 10.5 and 1.5 Hz). The multiplicity of nodal C-4a and C-8a changed to doublets upon substitution of one of the F atoms. Constant $^{3}J_{CF} \geq 10$ Hz was preserved for only one of them. Thus, the ^{13}C NMR spectrum of **Va** exhibited a doublet with δ_C 134.97 ppm (J_{CF} 12.9 Hz) and an unresolved singlet with δ_C 127.90 ppm. A weak-field doublet with δ_C 134.97 ppm was assigned to C-4a based on a 2D ^{1}H–^{13}C HMBC experiment (Fig. 1). In fact, this same C atom gave a cross-peak with proton H-3 (δ_H = 10.09 ppm) in the 2D ^{1}H–^{13}C HMBC spectrum. This was possible only for 7-substituted methylpiperazine derivative **Va**.

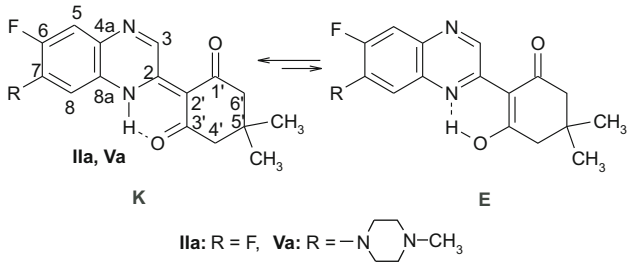
Thus, the combined NMR results suggested that **Va** – **c** were substitution products of F-7 by *N*-methylpiperazine.

Because products **V** were the principal substitution products from the reaction with *N*-methylpiperazine, it could be assumed that the CH-acidic functional group in the 2-position of compounds **II** activated F-7 of the aromatic quinoxaline core more toward amines.

Compounds **IIa** and **Va**, which contained a dimedone moiety in the 2-position of the quinoxaline ring, could theoretically exist in several tautomeric forms (Scheme 5). The PMR and ^{13}C NMR spectra lacked resonances indicating the existence in these solvents of the hypothetical tautomer in which dimedone C-2′ had sp^3-hybridization.

PMR spectra of **IIa** and **Va** in $CDCl_3$ solution gave a resonance for NH (or OH) as a narrow singlet that was shifted considerably to weak field (δ_H 18.3 and 17.4 ppm, respectively). This indicated that the molecules included a strong intramolecular H-bond (IMHB). The slight difference of the chemical shifts of dimedone C atoms C-1′ and C-3′ (δ_C = 1.8 ppm for **IIa** and 1.3 ppm for **Va**) argued in favor of tautomer **K**. Greater differences in the chemical shifts of the carbonyl C atoms could be expected for tautomer **E**. However, an analysis of 2D ^{1}H–^{13}C HMBC experiments was consistent with the presence of both tautomeric forms **K** and **E**.

Scheme 5



In fact, on one hand we observed cross-peaks between the NH proton and C-3, C-4a, and C-2 that were characteristic of tautomer **K**. On the other, the HMBC spectrum of **IIa** showed cross-peaks between a weak-field proton and C-3′ (194.35 ppm) and C-4′ (48.65 ppm) that either could occur in tautomer **E** or could be due to transfer of spin–spin coupling through an IMHB in tautomer **K**. In both instances, the strongest cross-peak corresponded to coupling of the NH proton and C-2′. However, such coupling could occur in both tautomeric forms.

We measured chemical shifts of ^{15}N through 2D ^{1}H–^{15}N HMQC and HMBC experiments in order to obtain additional information about the state of the tautomeric equilibrium for the studied compounds. In both instances, cross-peaks in ^{1}H–^{15}N HMQC spectra that were due to direct coupling of the NH proton and N-1 were observed. This left no doubt that the tautomeric equilibrium was shifted toward species **K**. Also, in our opinion, the measured ^{15}N chemical shifts for N-1 (δ_N 206 and 178 ppm, respectively) were intermediate between shifts of sp^3- and sp^2-hybridized N. Thus, the ranges of ^{15}N chemical shifts for these instances were 120 – 150 and 290 – 350 ppm according to the literature [9].

Considering the aforementioned, it could be assumed that tautomeric equilibrium in $CHCl_3$ solution was shifted toward tautomer **K**. However, tautomeric form **E** contributed noticeably to the equilibrium state.

Thus, substituents could be introduced sequentially into different parts of the quinoxaline core and new potentially biologically active derivatives could be obtained intentionally owing to the different lability of the H atoms in the heterocyclic ring and the F atoms in the aromatic fragment and the use of appropriate activation methods. Therefore, products from substitution of one of the F atoms by amines were of definite interest. These did in fact contain pharmacophores analogous to those in fluoroquinolone antibiotics [10].

EXPERIMENTAL PART

^{1}H, ^{19}F, and ^{13}C NMR spectra of **IIa** and **Va** were recorded on a Bruker Avance-500 instrument. The internal standard for ^{1}H and ^{13}C NMR spectra was TMS; for ^{19}F NMR spectra, hexafluorobenzene. Resonances in PMR and ^{13}C NMR spectra for **IIa** and **Va** were assigned based on 2D ^{1}H–^{13}C HSQC and HMBC experiments. PMR spectra of **IIb**

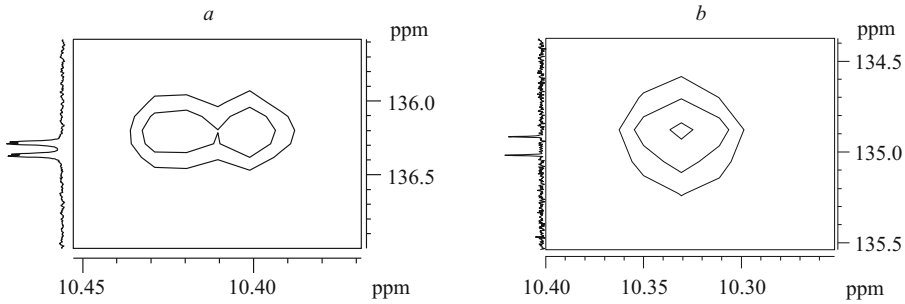


Fig. 1. Correlations between proton H-3 and nodal C-4a that were observed in 2D $^{1}H–^{13}C$ HMBC spectra of **IIa** (*a*) and **Va** (*b*).

and -**c** and **Vb** and -**c** were recorded in DMSO-d_6 on a DRX-400 spectrometer (FRG). Electron-impact mass spectra (MS-EI) were obtained on a Bruker Daltronics MicrOTOF-Q instrument at average ionizing potential 75 eV and 250°C.

Elemental analyses for the indicated empirical formulas agreed with those calculated.

2-(6,7-Difluoroquinoxalin-2(1*H*)-ylidene)-5,5-dimethylcyclohexane-1,3-dione (IIa). Compound **I** (0.166 g, 1.0 mmol) and dimedone (0.160 g, 1.14 mmol) in DMSO (1.5 mL) were stirred for 48 h at 23 – 25°C in the presence of HCl (conc., 0.1 mL). The precipitate of **IIa** was filtered off and washed with EtOH (1.5 – 2 mL). Yield 0.148 g (50%), mp 228 – 230°C.

PMR spectrum, δ, ppm: (500.1 MHz, $CDCl_3$): 18.27 (s, 1H, NH); 10.42 (s, 1H, H3); 7.85 (dd, 1H, $^{3}J_{H,F}$ = 10.1, $^{4}J_{H,F}$ = 8.0 Hz, H5); 7.53 (dd, 1H, $^{3}J_{H,F}$ = 9.7, $^{4}J_{H,F}$ = 7.5 Hz, H8); 2.64 (m, 2H, CH_2); 2.50 (s, 2H, CH_2); 1.15 (s, 6H, 2 · Me).

^{19}F NMR spectrum, $^{3}J_{F,F}$ (470.5 MHz, $CDCl_3$): 35.31 (ddd, $^{3}J_{F,F}$ = 21.3, $^{3}J_{H,F}$ = 9.7, $^{4}J_{H,F}$ = 8.0 Hz, F7); 30.25 (ddd, $^{3}J_{F,F}$ = 21.3, $^{3}J_{H,F}$ = 10.1, $^{4}J_{H,F}$ = 7.5 Hz, F6).

^{13}C NMR spectrum, $^{3}J_{F,F}$ (125.7 MHz, $CDCl_3$): 196.18 and 194.35 (C1′, C3′); 152.87 (dd, $^{1}J_{C,F}$ = 251.4, $^{2}J_{C,F}$ = 15.8 Hz, C6/C7); 150.81 (dd, $^{1}J_{C,F}$ = 255.1, $^{2}J_{C,F}$ = 15.2 Hz, C6/C7); 149.19 (d, $^{6}J_{C,F}$ = 2.1 Hz, C2); 148.04 (d, $^{6}J_{C,F}$ = 3.4 Hz, C3); 136.32 (dd, $^{3}J_{C,F}$ = 10.3, $^{4}J_{C,F}$ = 1.9 Hz, C4a); 129.31 (dd, $^{3}J_{C,F}$ = 10.5, $^{4}J_{C,F}$ = 1.5 Hz, C8a); 116.18 (Hz, $^{2}J_{C,F}$ = 22.3, $^{3}J_{C,F}$ = 2.1 Hz, C5); 108.97 (dd, $^{2}J_{C,F}$ = 20.0, $^{3}J_{C,F}$ = 1.3 Hz, C8); 104.85 (C2′); 52.82 (CH_2); 48.65 (CH_2); 30.91 (C5′); 28.26 (2 · Me).

^{15}N NMR spectrum, $^{3}J_{H,F}$ (50.7 MHz, $CDCl_3$): 336 (N-4); 206 (N-1).

Mass spectrum, *m/z* (I_{rel}, %): 304 [M^+] (73). $C_{16}H_{14}F_2N_2O_2$.

2-(6,7-Difluoroquinoxalin-2(1*H*)-ylidene)-2*H*-indene-1,3-dione (IIb). Compound **I** (0.083 g, 0.5 mmol) and indandione (0.140 g, 0.98 mmol) in DMSO (1.5 mL) were stirred for 48 h at 20 – 25°C in the presence of HCl (conc., 0.05 mL). The resulting precipitate was filtered off and washed with EtOH (2 mL). [6, R. p. 49].

Yield 0.066 g (44%). mp > 300°C. PMR spectrum, δ, ppm: 7.73 (s, 4H, CH_{arom}); 8.00 – 8.10 (m, 1H, $CH_{arom\text{-}quinoxalin}$); 8.30 – 8.36 (m, 1H, $CH_{arom\text{-}quinoxalin}$), 9.97 (s, 1H, $CH_{quinoxalin}$). Mass spectrum, *m/z* (I_{rel}, %): 310 [M^+] (100). $C_{17}H_8N_2F_2O_2$.

4-(6,7-Difluoroquinoxalin-2(1*H*)-ylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (IIc). Compound **I** (0.166 g, 1.0 mmol) and pyrazolone (0.175 g, 1.0 mmol) in DMSO (1.5 mL) were stirred for 48 h at 20 – 25°C in the presence of HCl (0.1 mL). The resulting precipitate was filtered off and washed with EtOH (2 mL). [7, R. p. 49].

Yield 0.160 g (47%). mp 230 – 232°C. PMR spectrum, δ, ppm: 2.64 (c, 3H, CH_3), 7.20 – 7.30 (m, 1H, CH_{arom}), 7.40 – 7.50 (m, 2H, CH_{arom}), 7.80 – 7.90 (m, 2H, CH_{arom}), 7.90 – 8.00 (m, 1H $CH_{quinoxalin}$), 8.00 – 8.20 (m, 1H, $CH_{quinoxalin}$), 9.38 (br.s, 1H, $CH_{quinoxalin}$). Mass spectrum, m/z (I_{rel}, %): 338 [M^+] (100). $C_{18}H_{12}N_4F_2O_2$.

4-(6,7-Difluoroquinoxalin-2-yl)benzene-1,3-diol (IId). Compound **I** (0.166 g, 1.0 mmol) and resorcinol (0.135 g, 1.2 mmol) in anhydrous EtOH (5 mL) were refluxed for 5 h in the presence of HCl (conc., 0.2 mL), diluted with H_2O (1:1), and cooled to 15 – 20°C. The precipitate of **IId** was filtered off. [8, R. p. 49].

Yield 0.055 g (25%). mp > 250°C. PMR spectrum (DMSO-d_6), δ, ppm: 6.37 (d, 1H, J 2.3 Hz, CH_{arom}); 6.4 (dd, 1H, J 8.7 Hz, J 2.3 Hz, CH_{arom}); 7.80 – 7.96 (m, 1H, $CH_{quinoxalin}$); 7.97 – 8.03 (m, 1H, $CH_{quinoxalin}$); 8.03 (d, 1H, J 8.7 Hz, CH_{arom}); 9.56 (s, 1H, $CH_{quinoxalin}$); 9.87 (s, 1H, OH), 13.36 (s, 1H, OH). MS: m/z (I_{rel}, %): 274 [M^+] (100). $C_{14}H_8N_2F_2O_2$.

Reaction of I with 3-methyl-1-phenylpyrazol-5-one in the presence of base. Compound **I** (0.166 g, 1.0 mmol) and 3-methyl-1-phenylpyrazol-5-one (0.522 g, 3.0 mmol) in DMSO (2 mL) were held for 48 h at room temperature in the presence of TEA (0.3 mL), diluted with H_2O (1:1), and acidified with HCl solution (15%) until the pH was 5 – 6. The resulting precipitate was filtered off, washed with hot EtOH (10 mL), and dried at 100°C to afford **IV** (0.340 g, 47%), mp > 250°C. The EtOH rinsings were cooled. The resulting precipitate of **III** was filtered off. Yield 0.025 g (7%). Compound **III** was identified by melting point and spectral char-

acteristics (PMR, MS) as dipyrazolylmethane, which was described before [7, 8].

Transformation of IV into III

A. Compound **IV** (0.020 g, 0.03 mmol) was heated in refluxing DMF (2 mL) for 5 min, cooled to room temperature, and diluted with H_2O (1:1). The resulting precipitate of **III** was filtered off, yield 0.010 g (50%).

B. Compound **IV** (0.020 g, 0.03 mmol) was dissolved in DMF (1.5 mL) at room temperature, treated with I_2 (0.020 g, 0.08 mmol), held at room temperature for 24 h, and treated with H_2O (0.1 mL). The resulting precipitate of **III** was filtered off, yield 0.010 g (50%).

2-[6-Fluoro-7-(4-methylpiperazin-1-yl)quinoxalin-2-(1*H*)-ylidene]-5,5-dimethylcyclohexane-1,3-dione (Va). Compound **IIa** (0.060 g, 0.02 mmol) in DMF (1 mL) was heated with *N*-methylpiperazine (0.10 g, 1.0 mmol) at 120°C for 2.5 – 3 h and diluted with H_2O until crystalline **Va** precipitated. The precipitate of **Va** was filtered off and washed with H_2O. Yield 0.045 g (59%). mp 173 – 174°C. PMR spectrum (500.1 MHz, $CDCl_3$), δ, ppm: 17.43 (s, 1H, NH); 10.34 (s, 1H, H3); 7.64 (d, 1H, $^3J_{H,F}$ 13.0 Hz, H-5); 6.98 (d, 1H, $^4J_{H,F}$ 8.0 Hz, H-8); 3.33 (m, 4H, H-2″); 2.65 (m, 4H, H-3″); 2.59 (s, 2H, H-4′); 2.49 (s, 2H, H-6′); 2.39 (s, 3H, NMe); 1.13 (s, 6H, 2×Me). NMR spectrum ^{19}F (470, 5MHz, $CDCl_3$) δ, ppm: 44.44 (dd, $^3J_{H,F}$ 13.0, $^4J_{H,F}$ 8.0 Hz, F-6). NMR spectrum ^{13}C (125.7 MHz, $CDCl_3$) δ, ppm: 197.43 and 196.16 (C-1′, 3′); 155.41 (d, $^1J_{C,F}$ 253.7 Hz, C-6); 147.24 (d, $^6J_{C,F}$ 1.9 Hz, C-2); 145.63 (C-3); 144.93 (d, $^2J_{C,F}$ 11.2 Hz, C-7); 134.97 (d, $^3J_{C,F}$ 12.9 Hz, C-4a); 127.90 (C-8a); 114.66 (d, $^2J_{C,F}$ 22.4 Hz, C-5); 106.46 (d, $3J_{C,F}$ 4.4 Hz, C-8); 103.40 (C-2′); 54.73 (C-3″); 53.01 and 50.46 (C-4′,6′); 50.08 (d, $^4J_{C,F}$ 5.0 Hz, C-2″); 46.06 (NMe); 30.80 (C-5′); 28.33 (2×Me). NMR spectrum ^{15}N (50.7 MHz, $CDCl_3$) δ, ppm: 336 (N-4); 178 (N-1); 66 (N-1″); 37 (N-4″). Mass spectrum, m/z (I_{rel}, %): 384 [M^+] (36), 70 (100). $C_{21}H_{25}N_4FO_2$.

2-[6-Fluoro-7-(4-methylpiperazin-1-yl)quinoxalin-2(1*H*)-ylidene]-2*H*-indene-1,3-dione (Vb). Compound **IIb** (0.021 g, 0.07 mmol) in DMF (1 mL) was heated with *N*-methylpiperidine (0.10 g, 1.0 mmol) at 120°C for 2.5 – 3 h and filtered. The mother liquor was evaporated to dryness in vacuo. The solid was worked up with H_2O (1.5 – 2 mL). The residue of **Vb** was filtered off and washed with H_2O (1.5 – 2 mL). Yield 0.16 g (61%). mp > 250°C. PMR spectrum, δ, ppm: 2.33 (s, 3H, CH_3), 2.60 – 2.62 (m. 4H, 2×CH_2), 3.32 – 3.34 (m. 4H, 2×CH_2), 7.50 – 7.56 (m, 1H, $CH_{quinoxalin}$); 7.63 (m, 4H, CH_{arom}); 7.62 – 7.65 (m, 1H, $CH_{quinoxalin}$), 9.75 (s, 1H, $CH_{quinoxalin}$), 13.50 (br.s 1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 384 [M^+] (36), 70 (100). $C_{22}H_{19}N_4FO_2$.

4-[6-Fluoro-7-(4-methylpiperizin-1-yl)quinoxalin-2-(1*H*)-ylidene]-3-methyl-1-phenyl-(1*H*)-pyrazol-5(4*H*)-one (Vc). Compound **IIc** (0.067 g, 0.2 mmol) in DMF (1 mL) was heated with *N*-methylpiperazine (0.10 g, 1.0 mmol) at 120°C for 2.5 – 3 h and diluted with H_2O until crystalline **Vc** precipitated. The precipitate of **Vc** was filtered off and washed with H_2O. Yield 0.43 g (53%). mp 220 – 221°C. PMR spectrum, (DMSO-d_6), δ, ppm: 2.32 (s, 3H, CH_3), 2.53 (s. 3H, CH_3), 2.58 – 2.60 (m. 4H, 2×CH_2), 3.30 – 3.33 (m. 4H, 2×CH_2), 7.10 – 7.35 (m, 1H, $CH_{arom\text{-}quinoxalin}$); 7.33 – 7.40 (m, 2H, CH_{arom}); 7.50 – 7.54 (m, 1H, $CH_{arom\text{-}quinoxalin}$), 8.00 – 8.03 (m, 2H, CH_{arom}), 8.97 (s, 1H, $CH_{quinoxalin}$). Mass spectrum, m/z (I_{rel}, %): 418 [M^+] (47), 70 (100). $C_{23}H_{23}N_6FO$.

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REFERENCES

1. G. B. Barlin, *The Pyrazines*, in: *The Chemistry of Heterocyclic Compounds*, A. Weissberger and E. C. Taylor (eds.), Vol. 41, Wiley / Interscience, Chichester (1982).
2. G. W. N. Cheeseman and R. F. Cookson, *Condensed Pyrazines*, in: *The Chemistry of Heterocyclic Compounds*, A. Weissberger and E. C. Taylor (eds.), Vol. 35, Wiley / Interscience, New York (1979).
3. M. D. Mashkovskii, *Drugs* [in Russian], Meditsina, Moscow (1993), Part II, p. 356.
4. EP 0672662 (1995), Sept. 20, 1995; *Chem. Abstr.*, **124**, 55985 (1996).
5. V. N. Charushin, G. A. Mokrushina, and A. V. Tkachev, *J. Fluorine Chem.*, **107**, 71 – 80 (2001).
6. Yu. A. Azev and E. D. Oparina, *Khim. Geterotsikl. Soedin.*, No. 10, 1576 – 1578 (2011).
7. Yu. A. Azev, H. Neunhoeffer, S. Foro, et al., *Mendeleev Commun.*, 229 – 231 (1995).
8. Yu. A. Azev, E. D. Oparina, I. S. Kovalev, et al., *Mendeleev Commun.*, 37 – 38 (2012).
9. G. C. Levy and R. L. Lichter, *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*, Wiley, New York (1979).
10. M. I. Fadeeva, M. V. Shul'gina, and R. G. Glushakov, *Khim.-farm. Zh.*, **27**(5), 4 – 19 (1993); N. I. Fadeeva, M. V. Shulgina, and R. G. Glushkov, *Pharm. Chem. J.*, **27**(5), 295 – 315 (1993).